June 26, 2002

APPLICATION SERIAL NUMBER

09702841

DOES NOT COMPLY WITH THE SEQUENCE RULES. See reasons below.

The application is not in sequence rule compliance. A table on the CDR has been incorporated by reference (specification page 1, lines 5-10) per 37 C.F.R. 1.52 and 1.58.

The CDR contains a table but the table contains recitation of sequences embedded in the table. A sample of the first 6 pages of the table demonstrate the issue. Each of the sequences recited in the table need to be in a sequence listing (Paper or CDR) and in computer readable format per 37 CFR 1.821 – 1.825.

Protein Domain Table

Pfam Prosite Full Name Description

Nitrilases / cyanide hydratase signatures Nitrilases (EC 3.5.5.1) are enzymes that convert nitriles into their corresponding acids and ammonia. They are widespread in microbes as well as in plants where they convert indole-3-acetonitrile to the hormone indole-3-acetic acid. A conserved cysteine has been shown [1,2] to be essential for enzyme activity; it seems to be involved in a nucleophilic attack on the nitrile carbon atom. Cyanide hydratase (EC 4.2.1.66) converts HCN to formamide. In phytopathogenic fungi, it is used to avoid the toxic effect of cyanide released by wounded plants [3]. The sequence of cyanide hydrolase is evolutionary related to that of nitrilases. Yeast hypothetical proteins YIL164c and YIL165c also belong to this family. As signature patterns for these enzymes, two conserved regions were selected. The first is located in the N-terminal section while the second, which contains the active site cysteine, is located in the central section.

Consensus pattern: G-x(2)-[LIVMFY](2)-x-[IF]-x-E-x(2)-[LIVM]-x-G-Y-P-
Consensus pattern: G-[GAQ]-x(2)-C-[WA]-E-[NH]-x(2)-[PST]-[LIVMFYS]-x-[KR] [C is the active site residue]-

[1] Kobayashi M., Izui H., Nagasawa T., Yamada H. Proc. Natl. Acad. Sci. U.S.A. 90:247-251(1993).
[2] Kobayashi M., Komeda H., Yanaka N., Nagasawa T., Yamada H. J. Biol. Chem. 267:20746-20751(1992).
[3] Wang P., Vanetten H.D. Biochem. Biophys. Res. Commun. 187:1048-1054(1992).

Polypeptide deformylase [1]

Medline: 97002011
A new subclass of the zinc metalloproteases superfamily revealed by the solution structure of peptide deformylase.
Meinnel T, Blanquet S, Dardel F;
J Mol Biol 1996;262:375-386.
[2]Medline: 98332750
Solution structure of nickel-peptide deformylase.
Dardel F, Ragusa S, Lazennec C, Blanquet S, Meinnel T;
J Mol Biol 1998;280:501-513.
Number of members: 21

(Peptidase M17) Cytosol aminopeptidase signature

Cytosol aminopeptidase is a eukaryotic cytosolic zinc-dependent exopeptidase that catalyzes the removal of unsubstituted amino-acid residues from the N-terminus of proteins. This enzyme is often known as leucine aminopeptidase (EC 3.4.11.1) (LAP) but has been shown [1] to be identical with prolyl aminopeptidase (EC 3.4.11.5). Cytosol aminopeptidase is a hexamer of identical chains, each of which binds two zinc ions.
Cytosol aminopeptidase is highly similar to Escherichia coli pepA, a manganese dependent aminopeptidase. Residues involved in zinc ion-binding [2] in the mammalian enzyme are absolutely conserved in pepA where they presumably bind manganese.
A cytosol aminopeptidase from Rickettsia prowazekii [3] and one from Arabidopsis thaliana also belong to this family.
As a signature pattern for these enzymes, a perfectly conserved octapeptide was selected which contains two residues involved in binding metal ions: an aspartate and a glutamate.

-Consensus pattern: N-T-D-A-E-G-R-L [The D and the E are zinc/manganese ligands]
-Note: these proteins belong to family M17 in the classification of peptidases [4,E1].

[1] Matsushima M., Takahashi T., Ichinose M., Miki K., Kurokawa K., Takahashi K. Biochem. Biophys. Res. Commun. 178:1459-1464(1991).
[2] Burley S.K., David P.R., Sweet R.M., Taylor A., Lipscomb W.N. J. Mol. Biol. 224:113-140(1992).
[3] Wood D.O., Solomon M.J., Speed R.R. J. Bacteriol. 175:159-165(1993).
[4] Rawlings N.D., Barrett A.J. Meth. Enzymol. 248:183-228(1995).

Assemblin (Peptidase family S21)

[1]
Medline: 96399137
Three-dimensional structure of human cytomegalovirus protease.
Shieh HS, Kurumbail RG, Stevens AM, Stegeman RA, Sturman EJ, Pak JY, Wittwer AJ, Palmier MO, Wiegand RC, Holwerda BC, Stallings WC;
Nature 1996;383:279-282.
Number of members: 29

Pollen proteins Ole e I family signature

The following plant pollen proteins, whose biological function is not yet known, are structurally related [1]:
- Olive tree pollen major allergen (Ole e I).
- Tomato anther-specific protein LAT52. - Maize pollen-specific protein ZmC13.
These proteins are most probably secreted and consist of about 145 residues. As shown in the following schematic representation, there are six cysteines which are conserved in the sequence of these proteins. They seem to be involved in disulfide bonds.

xxxxxxCxCxxxxxxxxxxCxxxxxxxxxxxxxxxxxxCxxxxxCxxxxxxxxxxxxxxxxxxxxxCxxxxxxx
******'C': conserved cysteine involved in a disulfide bond.
'*': position of the pattern.

-Consensus pattern: [EQ]-G-x-V-Y-C-D-T-C-R [The two C's are probably involved in disulfide bonds]

[1] Villalba M., Batanero E., Lopez-Otin C., Sanchez L.M., Monsalve R.I., Gonzalez De La Pena M.A., Lahoz C., Rodriguez R. Eur. J. Biochem. 216:863-869(1993).

Pollen allergen

This family contains allergens lol PI, PII and PIII from Lolium perenne.
Number of members: 49

[1]
Medline: 90105394
Complete primary structure of a Lolium perenne (perennial rye grass) pollen allergen, Lol p III: comparison with known Lol p I and II sequences.
Ansari AA, Shenbagamurthi P, Marsh DG;
Biochemistry 1989;28:8665-8670.

Porphobilinogen deaminase cofactor-binding site

Porphobilinogen deaminase (EC 4.3.1.8), or hydroxymethylbilane synthase, is an

enzyme involved in the biosynthesis of porphyrins and related macrocycles. It catalyzes the assembly of four porphobilinogen (PBG) units in a head to tail fashion to form hydroxymethylbilane.
The enzyme covalently binds a dipyrromethane cofactor to which the PBG subunits are added in a stepwise fashion. In the Escherichia coli enzyme (gene hemC), this cofactor has been shown [1] to be bound by the sulfur atom of a cysteine. The region around this cysteine is conserved in porphobilinogen deaminases from various prokaryotic and eukaryotic sources.

-Consensus pattern: E-R-x-[LIVMFA]-x(3)-[LIVMF]-x-G-[GSA]-C-x-[IVT]-P-[LIVMF]-[GSA] [C is the cofactor attachment site]

[1] Miller A.D., Hart G.J., Packman L.C., Battersby A.R. Biochem. J. 254:915-918(1988).

Presenilin

Mutations in presenilin-1 are a major cause of early onset Alzheimer's disease [2]. It has been found that presenilin-1 (Swiss:P49768) binds to beta-catenin in vivo [4]. This family also contains SPE proteins from C.elegans.
Number of members: 23

[1]
Medline: 98045995
Presenilins and Alzheimer's disease.
Kim TW, Tanzi RE;
Curr Opin Neurobiol 1997;7:683-688.
[2]Medline: 98045995
Presenilins and Alzheimer's disease.
Kim TW, Tanzi RE;
Curr Opin Neurobiol 1997;7:683-688.
[3]Medline: 98099802
Interaction of presenilins with the filamin family of actin-binding proteins.
Zhang W, Han SW, McKeel DW, Goate A, Wu JY;
J Neurosci 1998;18:914-922.
[4]Medline: 99004850
Destabilisation of beta-catenin by mutations in presenilin-1 potentiates neuronal apoptosis.
Zhang Z, Hartmann H, Do VM, Abramowski D, Sturchler-Pierrat C, Staufenbiel M, Sommer B, van de Wetering M, Clevers H, Saftig P, De Strooper B, He X, Yankner BA;
Nature 1998;395:698-702.

(Pribosyltran) Purine/pyrimidine phosphoribosyl transferases signature

Phosphoribosyltransferases (PRT) are enzymes that catalyze the synthesis of beta-n-5'-monophosphates from phosphoribosylpyrophosphate (PRPP) and an enzyme specific amine. A number of PRT's are involved in the biosynthesis of purine, pyrimidine, and pyridine nucleotides, or in the salvage of purines and pyrimidines. These enzymes are:
- Adenine phosphoribosyltransferase (EC 2.4.2.7) (APRT), which is involved in purine salvage.
- Hypoxanthine-guanine or hypoxanthine phosphoribosyltransferase (EC 2.4.2.8) (HGPRT or HPRT), which are involved in purine salvage.
- Orotate phosphoribosyltransferase (EC 2.4.2.10) (OPRT), which is involved in pyrimidine biosynthesis.
- Amido phosphoribosyltransferase (EC 2.4.2.14), which is involved in purine biosynthesis.
- Xanthine-guanine phosphoribosyltransferase (EC 2.4.2.22) (XGPRT), which is involved in purine salvage.

In the sequence of all these enzymes there is a small conserved region which may be involved in the enzymatic activity and/or be part of the PRPP binding site [1].

-Consensus pattern: [LIVMFYWCTA]-[LIVM]-[LIVMA]-[LIVMFC]-[DE]-D-[LIVMS]-[LIVM]-[STAVD]-[STAR]-[GAC]-x-[STAR]
-Note: in position 11 of the pattern most of these enzymes have Gly.

[1] Hershey H.V., Taylor M.W. Gene 43:287-293(1986).

(Pro CA)

Prokaryotic-type carbonic anhydrases signatures

Carbonic anhydrases (EC 4.2.1.1) (CA) are zinc metalloenzymes which catalyze the reversible hydration of carbon dioxide. In Escherichia coli, CA (gene cynT) is involved in recycling carbon dioxide formed in the bicarbonate-dependent decomposition of cyanate by cyanase (gene cynS). By this action, it prevents the depletion of cellular bicarbonate [1]. In photosynthetic bacteria and plant chloroplast, CA is essential to inorganic carbon fixation [2]. Prokaryotic and plant chloroplast CA are structurally and evolutionary related and form a family distinct from the one which groups the many different forms of eukaryotic CA's (see <PDOC00146>). Hypothetical proteins yadF from Escherichia coli and HI1301 from Haemophilus influenzae also belong to this family. Two signature patterns were developed for this family of enzymes. Both patterns contain conserved residues that could be involved in binding zinc (cysteine and histidine).

-Consensus pattern: C-[SA]-D-S-R-[LIVM]-x-[AP]
-Consensus pattern: [EQ]-Y-A-[LIVM]-x(2)-[LIVM]-x(4)-[LIVMF](3)-x-G-H-x(2)-C-G

[1] Guilloton M.B., Korte J.J., Lamblin A.F., Fuchs J.A., Anderson P.M. J. Biol. Chem. 267:3731-3734(1992).
[2] Fukuzawa H., Suzuki E., Komukai Y., Miyachi S. Proc. Natl. Acad. Sci. U.S.A. 89:4437-4441(1992).

(Prolyl_oligopep)

Prolyl oligopeptidase family serine active site

The prolyl oligopeptidase family [1,2,3] consist of a number of evolutionary related peptidases whose catalytic activity seems to be provided by a charge relay system similar to that of the trypsin family of serine proteases, but which evolved by independent convergent evolution. The known members of this family are listed below.

- Prolyl endopeptidase (EC 3.4.21.26) (PE) (also called post-proline cleaving enzyme). PE is an enzyme that cleaves peptide bonds on the C-terminal side of prolyl residues. The sequence of PE has been obtained from a mammalian species (pig) and from bacteria (Flavobacterium meningosepticum and Aeromonas hydrophila); there is a high degree of sequence conservation between these sequences.
- Escherichia coli protease II (EC 3.4.21.83) (oligopeptidase B) (gene prtB) which cleaves peptide bonds on the C-terminal side of lysyl and argininyl residues.

- Dipeptidyl peptidase IV (EC 3.4.14.5) (DPP IV). DPP IV is an enzyme that removes N-terminal dipeptides sequentially from polypeptides having unsubstituted N-termini provided that the penultimate residue is proline.
- Yeast vacuolar dipeptidyl aminopeptidase A (DPAP A) (gene: STE13) which is responsible for the proteolytic maturation of the alpha-factor precursor.
- Yeast vacuolar dipeptidyl aminopeptidase B (DPAP B) (gene: DAP2).
- Acylamino-acid-releasing enzyme (EC 3.4.19.1) (acyl-peptide hydrolase). This enzyme catalyzes the hydrolysis of the amino-terminal peptide bond of an N-acetylated protein to generate a N-acetylated amino acid and a protein with a free amino-terminus.

A conserved serine residue has experimentally been shown (in E.coli proteaseII as well as in pig and bacterial PE) to be necessary for the catalytic mechanism. This serine, which is part of the catalytic triad (Ser, His, Asp), is generally located about 150 residues away from the C-terminal extremity of these enzymes (which are all proteins that contains about 700 to 800 amino acids).

Consensus pattern: D-x(3)-A-x(3)-[LIVMFYW]-x(14)-G-x-S-x-G-G-[LIVMFYW](2) [S is the active site residue] Sequences known to belong to this class detected by the pattern ALL, except for yeast DPAP A.

Note: these proteins belong to families S9A/S9B/S9C in the classification of peptidases [4].

[1] Rawlings N.D., Polgar L., Barrett A.J. Biochem. J. 279:907-911(1991).

[2] Barrett A.J., Rawlings N.D.

[3] Polgar L., Szabo E.

[4] Rawlings N.D., Barrett A.J. Meth. Enzymol. 244:19-61(1994).

(Pterin 4a)
Pterin 4 alpha carbinolamine dehydratase

Pterin 4 alpha carbinolamine dehydratase is aka DCoH (dimerisation cofactor of hepatocyte nuclear factor 1-alpha).

Number of members: 11

[1] Cronk JD, Endrizzi JA, Alber T; Medline: 97052967 "High-resolution structures of the bifunctional enzyme and transcriptional coactivator DCoH and its complex with a product analogue." Protein Sci 1996;5:1963-1972.

(Pyridox oxidase)
Pyridoxamine 5'-phosphate oxidase signature

Pyridoxamine 5'-phosphate oxidase (EC 1.4.3.5) is a FMN flavoprotein involved in the de novo synthesis of pyridoxine (vitamin B6) and pyridoxal phosphate. It oxidizes pyridoxamine-5-P (PMP) and pyridoxine-5-P (PNP) to pyridoxal-5-P. The sequences of the enzyme from bacterial (genes pdxH or fprA) [1] and fungal (gene PDX3) [2] sources show that this protein has been highly conserved throughout evolution.
PdxH is evolutionary related [3] to one of the enzymes in the phenazine biosynthesis protein pathway, phzD (also known as phzG). As a signature pattern, a highly conserved region was selected located in the C-terminal part of these enzymes.

-Consensus pattern: [LIVF]-E-F-W-[QHG]-x(4)-R-[LIVM]-H-[DNE]-R

[1] Lam H.-M., Winkler M.E. J. Bacteriol. 174:6033-6045(1992).
[2] Loubbardi A., Karst F., Guilloton M., Marcireau C. J. Bacteriol. 177:1817-1823(1995).
[3] Pierson L.S. III, Gaffney T., Lam S., Gong F. FEMS Microbiol. Lett. 134:299-307(1995).

(Pyrophosphatase)
Inorganic pyrophosphatase signature

Inorganic pyrophosphatase (EC 3.6.1.1) (PPase) [1,2] is the enzyme responsible for the hydrolysis of pyrophosphate (PPi) which is formed principally as the product of the many biosynthetic reactions that utilize ATP. All known Ppases require the presence of divalent metal cations, with magnesium conferring the highest activity. Among other residues, a lysine has been postulated to be part or close to the active site. PPases have been sequenced from bacteria such as Escherichia coli (homohexamer), thermophilic bacteria PS-3 and Thermus thermophilus, from the archaebacteria Thermoplasma acidophilum, from fungi (homodimer), from a plant, and from bovine retina. In yeast, a mitochondrial isoform of PPase has been characterized which seems to be involved in energy production and whose activity is stimulated by uncouplers of ATP synthesis.

The sequences of PPases share some regions of similarities. As signature patterns a region was selected that contains three conserved aspartates that are involved in the binding of cations.

-Consensus pattern: D-[SGDN]-D-[PE]-[LIVMF]-D-[LIVMGAC]
[The three D's bind divalent metal cations]

[1] Lahti R., Kolakowski L.F. Jr., Heinonen J., Vihinen M., Pohjanoksa K., Cooperman B.S. Biochim. Biophys. Acta 1038:338-345(1990).
[2] Cooperman B.S., Baykov A.A., Lahti R. Trends Biochem. Sci. 17:262-266(1992).

(Peptidase S26)
Signal peptidases I signatures.

Signal peptidases (SPases) [1] (aka leader peptidases) remove the signal peptides from secretory proteins. In prokaryotes three types of SPasesare known: type I (gene lepB) which is responsible for the processing of the majority of exported pre-proteins; type II (gene lsp) which only process lipoproteins, and a third type involved in the processing of pili subunits. SPase I (EC 3.4.21.89) is an integral membrane protein that is anchored in the cytoplasmic membrane by one (in B. subtilis) or two (in E. coli) N-terminal transmembrane domains with the main part of the protein protuding in the periplasmic space. Two residues have been shown [2,3] to be essential for the catalytic activity of SPase I: a serine and an lysine. SPase I is evolutionary related to the yeast mitochondrial inner membrane protease subunit 1 and 2 (genes IMP1 and IMP2) which catalyze the removal of signal peptides required for the targeting of proteins from the mitochondrial matrix, across the inner membrane, into the inter-membrane space [4].In eukaryotes the removal of signal peptides is effected by an oligomeric enzymatic complex composed of at least five subunits: the signal peptidase complex (SPC). The SPC is located in the endoplasmic reticulum membrane. Two components of mammalian SPC, the 18 Kd (SPC18) and the 21 Kd (SPC21) subunits as well as the yeast SEC11 subunit have been shown [5] to share regions of sequence similarity with prokaryotic SPases I and yeast IMP1/IMP2. Three signature